08 C 749

EXHIBIT B

JUDGE CASTILLO
MAGISTRATE JUDGE VALDEZ

US005061703C1

(12) EX PARTE REEXAMINATION CERTIFICATE (5595th)

United States Patent
Bormann et al.

(10) **Number: US 5,061,703 C1**
(45) **Certificate Issued: Nov. 7, 2006**

(54) **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

(75) Inventors: **Joachim Bormann**, Frankfurt (DE); **Markus R. Gold**, Nauheim (DE); **Wolfgang Schatton**, Eschborn (DE)

(73) Assignee: **Merz Pharma GmbH & Co. KGaA**, Frankfurt am Main (DE)

Reexamination Request:
No. 90/007,176, Aug. 18, 2004

Reexamination Certificate for:

Patent No.:	**5,061,703**
Issued:	**Oct. 29, 1991**
Appl. No.:	**07/508,109**
Filed:	**Apr. 11, 1990**

(30) **Foreign Application Priority Data**

Apr. 14, 1989 (EP) 89106657

(51) **Int. Cl.**

A61K 31/55	(2006.01)
A61K 31/445	(2006.01)
A61K 31/41	(2006.01)

(52) **U.S. Cl.** **514/212.01**; 514/325; 514/359
(58) **Field of Classification Search** 514/212.01, 514/325, 359
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,450,761 A 6/1969 Schneider

FOREIGN PATENT DOCUMENTS

EP	0293974	12/1988
JP	58-4718	1/1983

OTHER PUBLICATIONS

Translation of: Rote Liste 63 008 (1983).
Translation of: Rote Liste 63 009 (1984).
Translation of: Rote Liste 63 008 (1985).
Translation of: Rote Liste 63 005 (1987).
Translation of: Rote Liste 63 005 (1988).
Translation of: Rote Liste 63 006 (1989).
Translation of: Akatinol® Memantine Labeling (Apr. 1984).
Translation of: Akatinol® Memantine Labeling (Feb. 1988).
Translation of: Pschyrembel Klinisches Worterbuch [Clinical Dictionary] 1839–1840 (255th ed. 1986).
Translation of: Pschyrembel Klinisches Worterbuch [Clinical Dictionary] 1384 (255th ed. 1986).
Translation of: Pschyrembel Klinisches Worterbuch [Clinical Dictionary] 808 (255th ed. 1986).
Translation of: Deutsche medizinische Wochenschrift [German Medical Weekly] 109: 987–990 (1984).
Fünfgeld et al., Psychopharmacology, XVIth C.I.N.P. Congress, Munich, 27.23.08, p. 180 (Aug. 15–18, 1988).
Adolfsson et al., Aging vol. 7, pp. 441–451 (1978).
Castaigne et al., La Nouvelle Presse Médicale, *Etude clinique de l'action psycho-stimulante de l'amantadine*, 3(26):1663–1664 (Jun. 29, 1974).
Costall B. and Naylor R.J. (1975). Neuropharmacological studies on D 145 (1,3 dimethyl–5–aminoadamantan). Psychopharmacologia (Berl.) 43:53–61.
Fischer P.A., Jacobi R., Scheider E. and Schonberger B. (1977). Die Wirkung Intravenoser Gaben von Memantin bei Parkinson–Kranken. Arzneim. Forsch./Drug. Res. 27 (II) Nr. 7, 1487.
Maj J., Sowinska H., Baran L. and Samek J. (1974). Pharmacological effects of 1,3–dimethyl–5–aminoadamantane, a new Adamantane derivative. Europ. J. Pharmacology 26, 9–14.
Schubert & Fleischhacker, Arztliche Praxis, XXXI, No. 46, vol. 9, pp. 2157–2160 (Jun. 1979).
Erkulwater and Pillai, Southern Med. J., 82: 550–553 (May 1989).
Moos, Medicinal Research Reviews; 8: 353–91 (1988).
Sieb et al., Dtch. Med. Wschr.; 112: 769–72 (1987).
Danielczyk, Psychiatria Danubina; 1: 71–75 (1989).
Kugler, Munich. Med. Wschr.; 127: 974–77 (1985).
Stetzer, Med. Welt; 35: 291–295 (Mar. 2, 1984).
Wallnofer and Schiller, Med. Welt.; 25: 703–706 (1974).
Pandeya, Indian J. Pharmacy.; 33: 1–9 (Jan.–Feb. 1971).
Bruseghini et al., IIe renunion luso–espagnole de pharmacologie, II Congreso Nacitonal de Quimica Terapeutica; Madrid (1982).

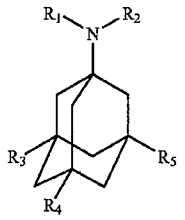
(Continued)

Primary Examiner—Kevin E. Weddington

(57) **ABSTRACT**

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula

(I)



wherein

R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof, is disclosed.

OTHER PUBLICATIONS

Burkhard et al., Institute of Chemical Technology Prague, pp. 91–97 (1973).
Meldrum et al., Naunyn–Schmiedeberg's Arch Pharmacol, 332:93–97 (1986).
Chojnacka–Wojcik et al., Pol. J. Pharmacol. Pharm. 35: 511–515 (1983).
Falbe et al., Rompp Chemie Lexikon, pp. 141, 151 (1989).
Berkow, Merck Manual, 14th ed. pp. 1324–1331(1982).
Otomo, Journal of Clinical Medicine, 7:127–132 (1988).
Tempel, D. Therapiewoche, 39 (14): 946–952 (Apr. 2, 1989).
Schäfer & Thiery, Psycho, 10:851–852 (1984).
Fröstl & Maitre, Pharmacopsychiat., 22: 54–100 (Supplement) (1989).
Koch, "Pharmakologie von Memantine" (1987).
Zimmerman, "Memantine—Ein neues Prinzip in der Geriatrie" (1987).
Tempel, "Ergebnisse einer Pilotuntersuchung mit zwei Dosisstufen von Memantine in der Geriatrie" (1988).
Tempel, "Memantine—Klinische Prüfungen in der Geriatrie" (1987).
Marcea, "Kooperationsmöglichkeiten zwischen Klinik und niedergelassenen Ärzten bei der Rehabilitation von Alterspatientien" (1987).
Rote Liste 63 008 (1983).
Rote Liste 63 009 (1984).
Rote Liste 63 008 (1985).
Rote Liste 63 005 (1987).
Rote Liste 63 005 (1988).
Rote Liste 63 006 (1989).
Akatinol® Memantine Labeling (Apr. 1984).
Akatinol® Memantine Labeling (Feb. 1988).
Pschyrembel Klinisches Worterbuch [Clinical Dictionary] 1839–1840 (255th ed. 1986).
Pschyrembel Klinisches Worterbuch [Clinical Dictionary] 1384 (255th ed. 1986).
Pschyrembel Klinisches Worterbuch [Clinical Dictionary] 808 (255th ed. 1986).
Olney et al., *European Journal of Pharmacology* 142:319–320 (1987).
Deutsche medizinische Wochenschrift [German Medical Weekly] 109: 987–990 (1984).
SCIENCE, vol. 226, pp. 850–852 (1984).
Cotman et al., Annual Review of Neuroscience, 11:61–80 (1988).
Rothman & Olney, Annals of Neurology, 19(2):108 (Feb. 1986).
Kemp et al., TINS, 10(7):294–298 (1987).
EP Application No. 89106657 (originally filed application for EP 0392059).
Response from Merz to EPO on Feb. 6, 1992.
EPO Examination Report dated Oct. 21, 1991.
Katzman, Alzheimer's Disease: Senile Dementia and Related Disorders, vol. 7, pp. 197–211 (1978).
Hahn et al., *Proc. Natl. Acad. Sci.*, 85:6556–6560 (1988).
Ingvar et al., Aging vol. 70, pp. 203–211 (1978).
Rote Liste, 63 008 (1986).
Marcea et al. Therapiewoche, 38:3097–3100 (1988).
Fleischhacker et al., Progress in Neuro–Psychopharmacology & Biological Psychiatry, 10:87–93 (1986).
Ambrozi et al., Pharmacopsychiatry, 21:144–146 (1988).

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

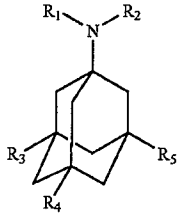
AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **1** and **10** are determined to be patentable as amended.

Claims **2–9** and **11–13**, dependent on an amended claim, are determined to be patentable.

New claims **14–19** are added and determined to be patentable.

1. A method for the prevention or treatment of cerebral ischemia comprising the step of *orally* administering, to a patient *diagnosed with Alzheimer's disease and* in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; *and*

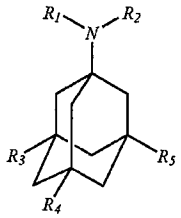
wherein

R_1, R_2, R_3, R_4 and R_5 do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

10. A method according to claim **1** for the treatment of Alzheimer's disease *wherein said adamantane derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg.*

14. A method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; and

wherein

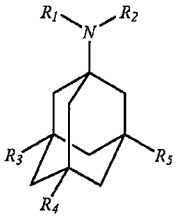
R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

15. The method of claim 14, wherein said adamantane derivative is memantine.

16. The method of claim 14, wherein said effective amount is from about 0.01 to 100 mg/kg.

17. A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

18. The method of claim 17, wherein said adamantane derivative in memantine.

19. The method of claim 17, wherein said effective amount is from about 0.01 to 100 mg/kg.

* * * * *